PATENT COOPERATION TREATY

From the:
INTERNATIONAL SEARCHING AUTHORITY

To:

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PCT

WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY

(PCT Rule 43*bis*.1)

	Date of mailing *(day/month/year)* - 8 DEC 2004
Applicant's or agent's file reference 502895	**FOR FURTHER ACTION** See paragraph 2 below

International application No.	International filing date *(day/month/year)*	Priority date *(day/month/year)*
PCT/AU2004/001456	22 October 2004	24 October 2003

International Patent Classification (IPC) or both national classification and IPC
Int. Cl.[7] G01N 33/68, A61K 31/00

Applicant
IMMUNAID PTY LTD et al

1. This opinion contains indications relating to the following items:

- [X] Box No. I — Basis of the opinion
- [ ] Box No. II — Priority
- [ ] Box No. III — Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
- [ ] Box No. IV — Lack of unity of invention
- [X] Box No. V — Reasoned statement under Rule 43*bis*.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
- [ ] Box No. VI — Certain documents cited
- [ ] Box No. VII — Certain defects in the international application
- [X] Box No. VIII — Certain observations on the international application

2. **FURTHER ACTION**

If a demand for international preliminary examination is made, this opinion will be considered to be a written opinion of the International Preliminary Examining Authority ("IPEA") except that this does not apply where the applicant chooses an Authority other than this one to be the IPEA and the chosen IPEA has notified the International Bureau under Rule 66.1*bis*(b) that written opinions of this International Searching Authority will not be so considered.

If this opinion is, as provided above, considered to be a written opinion of the IPEA, the applicant is invited to submit to the IPEA a written reply together, where appropriate, with amendments, before the expiration of 3 months from the date of mailing of Form PCT/ISA/220 or before the expiration of 22 months from the priority date, whichever expires later.

For further options, see Form PCT/ISA/220.

3. For further details, see notes to Form PCT/ISA/220.

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WRITTEN OPINION OF THE
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Box No. I Basis of the opinion

1. With regard to the **language,** this opinion has been established on the basis of the international application in the language in which it was filed, unless otherwise indicated under this item.

   ☐ This opinion has been established on the basis of a translation from the original language into the following language , which is the language of a translation furnished for the purposes of international search (under Rules 12.3 and 23.1(b)).

2. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application and necessary to the claimed invention, this opinion has been established on the basis of:

   a. type of material

      ☐ a sequence listing

      ☐ table(s) related to the sequence listing

   b. format of material

      ☐ in written format

      ☐ in computer readable form

   c. time of filing/furnishing

      ☐ contained in the international application as filed.

      ☐ filed together with the international application in computer readable form.

      ☐ furnished subsequently to this Authority for the purposes of search.

3. ☐ In addition, in the case that more than one version or copy of a sequence listing and/or table relating thereto has been filed or furnished, the required statements that the information in the subsequent or additional copies is identical to that in the application as filed or does not go beyond the application as filed, as appropriate, were furnished.

4. Additional comments:

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Box No. V **Reasoned statement under Rule 43*bis*.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement**

1. Statement

Novelty (N)	Claims	**9, 17, 31**	**YES**
	Claims	**1-8, 10-16, 18-30, 32-44**	**NO**
Inventive step (IS)	Claims	**9, 17, 31**	**YES**
	Claims	**1-8, 10-16, 18-30, 32-44**	**NO**
Industrial applicability (IA)	Claims	**1-44**	**YES**
	Claims		**NO**

2. Citations and explanations:

The following documents identified in the International Search Report have been considered for the purposes of this report:

D1: WO 2002/013828
D2: WO 2003/068257
D3: North, R. J. and Awward A. (1990) *Immunology* 71: 90-95
D4: Plana, M. *et al.* (2000) *AIDS* 14: 1921-1933
D5: WO 2001/008702
D6: US 6107020

Novelty (N) claims 1-8, 10-16, 18-30, 32-44

D1 teaches specific targeting of the 'regulator cell' population (eg. $CD4^+$ cells) in subjects infected with retroviruses while maintaining the population of 'effector cells' (eg. $CD8^+$ cells). Methods include the use of agents effective against the expanding regulator cell population at such a time that the activity of the effector cells is not significantly reduced (see page 3 lines 8-19, pages 4 second paragraph to page 5, and the section 'Agents which inhibit the production of and/or destroy regulator cells' which starts on page 7). Appropriate times for administering the agent to ablate regulator cells are provided and these include consideration of the viral load and $CD8^+$ and $CD4^+$ cell counts (see section 'Timing of exposing the subject to the agent' commencing page 7). Initiation of a new effector immune response is described using retroviral antigens, to facilitate subsequent ablation of the regulator cells response (page 3 line 30 to page 4 line 4 and page 9 line 22 to page 13 line 21). The disclosure of this document anticipates the invention of claims 1-6, 10-15, 20-30, 32, 35-44, rendering it not novel.

D2 teaches the specific targeting of the regulator cell population (eg. $CD4^+$ cells) in subjects with cancer. Methods include the use of agents effective against the expanding regulator cell population at such a time that the activity of the effector cells is not significantly reduced (see page 3 line 19 to page 4 line 8 and page 9-10 under 'Agents which inhibit the production of, limit the function of and/or destroy regulator cells'). Appropriate times for administering the agent to ablate regulator cells are provided and these include consideration of $CD8^+$ and $CD4^+$ cell counts, or measurements of a tumour or an inflammatory marker (see section 'Timing of exposing the subject to the agent' commencing page 10 and Examples 2-5). Initiation of a new effector immune response is described using tumour antigen, to facilitate subsequent ablation of the regulator cells response (page 3 line 30 to page 4 line 8 and page 5 lines-34). The disclosure of this document anticipates the invention of claims 1-3, 6-8, 10-16, 18-28, 32-44, which is therefore not novel.

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Box No. VIII Certain observations on the international application

The following observations on the clarity of the claims, description, and drawings or on the question whether the claims are fully supported by the description, are made:

Claims 1-8, 10-16, 18-30, 32-44 do not define the invention described.

The invention appears to relate to the applicants finding that the immune system is cycling during disease states characterised by the presence of regulator cells. Treatment of such a disease may be facilitated by targeting a specific phase of this cycle when specific inhibition of the regulator cells can be achieved while effector cell numbers against a cellular or viral cell antigen are maintained. (See for instance page 3 lines 6-8, 16-21 and page 4 lines 21-29.

However the majority of the claims, as specified above, make no reference to treatment with regard to a cycling immune system. References to 'determining *when* an agent should be administered' and similar phrases may also refer to the need for treatment *when* an individual has the disease or *when* an individual has a combination of symptoms and/or abnormalities in virological, biochemical or haematological parameters.

The failure to precisely define the invention in the claims has lead to the accompanying novelty and inventive step objections.

Supplemental Box

In case the space in any of the preceding boxes is not sufficient.

Continuation of: Box V

D3 describes the use of Vinblastine in a model of immunotherapy of advanced lymphoma based on the selective elimination of cycling (replicating) tumour-induced suppressor T cells (see Abstract). The article demonstrates that administration of the drug at such a time that replicating $CD4^+$ suppressor T cells are eliminated while non-replicating $CD8^+$ effector cells are spared, induced regression of L5178Y lymphoma in BDF1 mice which had not previously been treated for the disease, in the light of which claims 42 and 43 are not novel.

D4 demonstrates that restoration of the immune system can be achieved when highly active antiretroviral therapy (HAART) is initiated at very early stages of asymptomatic chronic HIV-1 infection (see Abstract and last paragraph of the Discussion). The method provided for determining when the agent should be administered includes monitoring the patient using measurements of CD4 and CD8 cells and plasma viral load (see Materials and Methods section). Plana *et al.* also describe the characteristic clinical features of HIV (loss of CD4 T lymphocytes, activation of CD8 and CD4 T lymphocytes and HIV replication, see Introduction, 1st paragraph), providing a means of diagnosing the disease. The teaching of this document is novelty-destroying for the broadly drafted claims 1, 3-6, 10, 12, 14, 18, 25, 26, 32, 35-40 and 44.

D5 discloses the use of immunotherapy in a human infected with an HIV or HTLV-1 retrovirus when viral load is less than 10,000 viral copies and $CD4^+$ cell count is above 500 cells/mL, the method comprising administering a nucleic acid based vaccine encoding HIV- or HTLV-specific peptides, to stimulate a protective $CD8^+$ response (see claim 1). The matter in this document renders claims 1-6, 10, 12, 14, 25, 27, 28, 37, 38 and 44 not novel.

D6 provides methods and kits for diagnosing the presence of retroviral disease including HIV, comprising correlating the rate of CD4% decline, cell-mediated cytotoxicity and plasma HIV RNA load, together with a staging system to suggest the most appropriate therapeutic intervention for a patient (see column 2 1st paragraph and claims). D6 renders the invention of claims 26 and 44.

In summary, claims 1-8, 10-16, 18-30, 32-44 lack novelty when compared with the above-listed documents.

Inventive Step (IS) 1-8, 10-16, 18-30, 32-44

Claims 1-8, 10-16, 18-30, 32-44 also lack an inventive step for the reasons given above.